accounting for 21.2% and 16.2% of total AED consumption (DDD 163.7 and 125.2, respectively). In the same year, oxcarbazepine and lamotrigine were the most used new AEDs (10.91% and 10.79% of total; DDD 84.1 and 83.2, respectively), while gabapentin and pregabalin exhibited the higher incidence of use. The main indication of use was epileptic disorders for older AEDs and neuropathic pain for newer AEDs. A high number of patients treated with older AEDs, in particular carbamazepine, phenobarbital, and valproic acid, received coprescription at clinically relevant interaction risk. Among newer AEDs, lamotrigine showed a high annual rate of possible interaction.
Conclusion: Significant differences were shown in the prescribing pattern of newer and older medications: older AEDs were mainly used in the treatment of epileptic disorders, while newer compounds were also preferred for conditions other than epilepsy, in particular neuropathic pain. The fall in the use of newer AEDs during 2007 agreed with revised reimbursement criteria for gabapentin and pregabalin. The coprescription should be evaluated with caution and avoided if possible. Drugs at risk of interactions should be replaced with others having same indication of use.
Disclosure of Interest: None declared.

PP179—IDENTIFICATION OF DRUG–DRUG INTERACTIONS THROUGH A DIGITAL HEALTH SERVICE

S. Ussai[1*]; A. Casetta[2]; F. Pisa[1]; G. Trillò[3]; R. Petelin[4]; F. Barbone[1,2]; A. Degrassi[4]; and G. Giagnorio[5]
[1]Institute of Hygiene and Clinical Epidemiology, University Hospital of Udine; [2]Dept. of Medical and Biological Sciences, University of Udine; [3]Helicopter Emergency Medical Service Friuli-Venezia Giulia, Udine Hospital, Udine; [4]R&D Department, Infostruttura Research Organization; and [5]Dept. of Emergency and Disaster Medicine, Ass.2 'Isontina', Gorizia, Italy
Introduction: Drug–drug interactions (DDIs) may have severe and life-threatening health consequences. To identify DDIs, a cloud-based surveillance has been implemented in a network of 12 pharmacies, 1 general hospital, and 24 general physicians of the ASS2 Health District, North East Italy.
Patients (or Materials) and Methods: DDIs were identified through a fully automated, closed loop system that records and updates, by specifically designed software interfaces loaded on Information and Communication Technology (ICT) programs of the network, all the drugs taken during therapy cycle/s. Each patient, agreeing to participate, was linked through her/his tax code to all prescription/OTC drugs managed from October 2012 to March 2013, generating a personal pharmacologic profile. Data on age, sex, and comorbidity were collected in the beginning of the study. DDIs were identified and classified according to Mario Negri Institute definition in 3 severity groups: low (no suspension or change in therapy required), moderate (change in treatment, additional therapy or hospitalization required), and high (potentially fatal).
Results: A total of 369 patients (58.3% women) were included. About 30% shown 1 comorbidity and 11.8% 2 or more. Cardiovascular diseases (22.7%) represented the most frequent comorbidity, followed by musculoskeletal pathology (13.6%), diabetes (8.6%), cancer (5.1%), and depression (4.8%). The Charlson Comorbidity Index was 0 in 65.2%, 1 in 25.7%, 2 in 7.0% and 3 to 4 in 2.1%. A total of 67 patients (mean age, 72 [12] years; 52.2% women) had at least 1 DDI. About 50% (N = 33) had up to 2 DDIs, 25% from 3 to 7 DDIs and 25% ≥8 (from 9–74 DDIs per person). A total of 501 DDIs were identified: the severity was low in 35.5%, moderate in 59.7% and high in 4.8%. The top 10 drugs involved in DDI were: acetylsalicylic acid (ASA), hydrochlorothiazide, ibuprofen, diclofenac, digoxin, nebivolol, pantoprazole, ramipril, furosemide, and nimesulide. DDIs occured more frequently with ASA and hydrochlorothiazide (6.2%), hydrochlorothiazide and pantoprazole (4.6%), ASA and ibuprofen (3.4%), ASA and nebivolol (3.4%), and ASA and nitroglycerin (3.2%). About 50% of DDIs involving ASA, hydrochlorothiazide, and ibuprofen were of low severity and another 50% of moderate severity. For diclofenac, low severity DDIs were 27.6% and 72.4% moderate while for digoxin 75.7% were moderate and 24.3% high.
Conclusion: ICT technologies are useful to timely identify DDIs of clinical relevance and the drugs most frequently involved.
Disclosure of Interest: None declared.

PP180—ROLE OF ORGANIC ANION TRANSPORTING POLYPEPTIDES 1A2 AND 2B1 IN CELLULAR UPTAKE OF NADOLOL

S. Misaka[*]; F. Müller; H. Glaeser; J. König; and M.F. Fromm
Institute of Experimental and Clinical Pharmacology and Toxicology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
Introduction: Due to its high solubility and low permeability, nadolol, a nonselective β-blocker, is categorized as a class III drug in a Biopharmaceutics Classification System, and therefore nadolol may require active influx transporters to permeate gut wall mucosa during intestinal absorption. Members of the organic anion transporting polypeptide (OATP) family such as OATP1A2 and OATP2B1 have previously been reported to be involved in intestinal absorption of several drugs. However, the molecular mechanism of nadolol uptake into enterocytes still remains unknown.
Patients (or Materials) and Methods: Human embryonic kidney (HEK) 293 cell lines stably expressing OATP1A2 or OATP2B1 were used to investigate whether nadolol is a substrate for these transporters using [3H]nadolol. Epigallocatechin 3-gallate (EGCG), a flavonoid highly abundant in green tea, was used as an inhibitor of OATP1A2- and OATP2B1-mediated transport.
Results: No significant nadolol uptake was observed in OATP2B1-expressing cells. In contrast, the uptake of nadolol in OATP1A2-expressing cells was significantly greater than that in vector-transfected cells. OATP1A2-mediated nadolol uptake was saturable with *K*m and *V*max values of 84.3 (1.0) μM and 332.8 (125.5) pmol/min/mg protein, respectively. OATP1A2-mediated uptake of nadolol was inhibited in a concentration dependent manner by EGCG with an *IC*50 value of 37.3 (5.9) μM.
Conclusion: These data suggest that OATP1A2 is predominantly involved in the cellular uptake of nadolol, while the role of OATP2B1 may be negligible. The inhibition of OATP1A2-mediated nadolol uptake might be involved in drug–drug and drug–food interactions with this β-blocker.
Disclosure of Interest: None declared.

PP181—EVALUATION OF THE INTERACTION BETWEEN METHOTREXATE AND PROTON PUMP INHIBITORS USING HUMAN OAT1 AND OAT3 HEK TRANSFECTED CELLS

R. Chioukh[1*]; M.-S. Noel-Hudson[1]; S. Ribes[1]; N. Fournier[2]; L. Becquemont[3]; and C. Verstuyft[4]
[1]EA 4123 Barrières physiologiques et réponses thérapeutiques; [2]UMR1154 Lipides Membranaires et Régulation Fonctionnelle du Coeur et des Vaisseaux, Université Paris XI Sud, Chatenay-Malabry; [3]Unite de Recherche Clinique (URC); and [4]Service de Génétique Moléculaire, Pharmacogénétique et Hormonologie, Université Paris XI Sud, Assistance Publique Hôpitaux de Paris, Hôpital Bicêtre, France

Introduction: In cancer patients, coadministration of methotrexate (MTX) and proton pump inhibitors (PPIs) can cause a pharmacokinetic interaction for delayed elimination and a subsequent increase in blood MTX concentration. Human organic anion transporters hOAT1 (*SLC22A6*) and hOAT3 (*SLC22A8*) are responsible for renal tubular secretion of MTX. We hypothesized that they are involved in drug interaction of MTX with PPIs. The aim of this study was to evaluate the inhibitory potencies of PPIs on HEK-hOAT1 and HEK-hOAT3 attempt to give an explanation to this possible drug–drug interaction between MTX and PPIs.
Patients (or Materials) and Methods: Uptake experiments were performed using HEK Flp-In 293, stably expressing human OAT1*(SLC22A6)* or OAT3 *(SLC22A8)*, by using the Flp-In™ System recombinase (Invitrogen®). We analyzed whether the inhibitory potencies of omeprazole, lansoprazole, and pantoprazole on OAT-mediated [3H] MTX uptake in vitro.
Results: MTX shown to be a high-affinity substrate for hOAT3 but not for hOAT1 (hOAT3 Km = 21.17 [5.65] μM). All PPIs showed in vitro inhibition of hOAT transporters. For that purpose, PAH, and ES were selected for probing hOAT1 and hOAT3 activities. However, their IC50 values concerning hOAT1 were 10 to 30 times higher than the unbound plasma concentrations of the PPIs. Conducted in parallel [3H]MTX uptake into HEK hOAT3 cells was inhibited by all PPIs in a concentration-dependent manner omeprazole, lansoprazole, and pantoprazole inhibit hOAT3, their IC50 were in the range of the therapeutic levels of the IPPs (0.91–8.06 μM).
Conclusion: PPIs significantly affect transport of MTX mediated by hOAT3, but this interaction cannot be explained by the inhibitory effects of PPIs on renal hOAT1. These in vitro results demonstrate that alterations of uptake transporters of MTX function by IPPs drugs have to be considered as potential mechanisms underlying drug–drug interactions between MTX-IPPs.
Disclosure of Interest: None declared.

PP183—EFFECT OF RITONAVIR, KETOCONAZOLE AND RIFAMPIN ON INTESTINAL AND HEPATIC CYTOCHROME P450 3A ENZYMES IN HEALTHY ASIAN ADULTS

K.-Y. Seng[1]; K.H. Hee[2]; and L.S.-U. Lee[2*]
[1]Pharmacology; and [2]Medicine, National University of Singapore, Singapore, Singapore

Introduction: Cytochrome P450 3A (CYP3A) is the major enzyme metabolizing drugs and xenobiotics in humans. The present study aimed to quantitate the extent of in vivo inhibition and induction effects of ritonavir, ketoconazole, and rifampin on the intestinal and hepatic activity of CYP3A in adult healthy Asians.
Patients (or Materials) and Methods: Fifteen healthy male or female Asian adults completed this open-label, single-center, sequential, partial crossover study. Subjects underwent 4 periods of treatments: baseline (reference) period; period 1, either ketoconazole 200 mg or ritonavir 100 mg twice daily given for 3 days; period 2, either ritonavir or ketoconazole given for 3 days (periods 1 and 2 in a randomized crossover design); period 3, rifampin 600 mg given nightly for 2 weeks. At the end of each period, each subject was administered with a single intravenous (IV) midazolam 0.75 mg, given in the fasting state, and a single oral 1.5-mg dose of midazolam 4 hours later. Serial blood samples were taken from the subjects at predose and at various time points for up to 12 hours after IV administration of midazolam. Concentrations of midazolam were measured using a validated LC/MS-MS approach. The hepatic midazolam clearance after IV dosing was directly modeled in NONMEM and was estimated separately for the reference and the test periods. The intestinal midazolam availability was calculated by dividing oral midazolam availability with hepatic midazolam availability. Formal interaction was excluded if the 90% CI for the ritonavir, ketoconazole, or rifampin over reference ratios for phenotyping metrics (hepatic midazolam clearance and intestinal midazolam availability) was within a 0.80 to 1.25 range.
Results: Ritonavir reduced hepatic and intestinal CYP3A activity to 0.68-fold (90% CI, 0.61–0.73) and to 0.36-fold (0.28–0.52), respectively. Ketoconazole reduced hepatic and intestinal CYP3A activity to 0.75-fold (90% CI, 0.69–0.81) and 0.52-fold (0.39–0.83), respectively. Rifampin increased hepatic and intestinal CYP3A activity by 1.22-fold (90% CI, 1.02–1.42) and 1.41-fold (1.04–2.19), respectively. There was a statistically significant and clinically relevant inhibition of the intestinal CYP3A activity due to chronic treatment with ritonavir.
Conclusion: Ritonavir treatment resulted in a clinically significant reduction in the net intestinal CYP3A activity. Extent of CYP3A inhibition produced by ketoconazole was smaller relative to ritonavir, especially at the intestinal level.
Disclosure of Interest: None declared.

PP186—THE ANALYSIS OF INTERACTION OF WARFARIN IN THE REAL CLINICAL PRACTICE

R. Barakanova*; and U. Tilekeeva
Basic and Clinical Pharmacology, Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan

Introduction: Estimation of prescription of warfarin (W) taking into account its interaction with other medicines in patients with coronary heart disease in clinical conditions.
Patients (or Materials) and Methods: The design of the research is retrospective. To estimate the level of polypharmacy and to analyze the interaction of W with other medicines medical documents of 61 patients with coronary heart disease have been analyzed. The effects of interaction of medicines were estimated according to BNF (British National Formulary) in March 2013. Estimation of the level of polypharmacy was considered according to the following 3 groups: 1, those who received 1 to 5 medicines. This shows rational use of medicines. 2, those who received 6 to 10 medicines; 3, those who received 11 to 15 medicines. The most clinically significant combinations of medicines have been analyzed.
Results: It has been established that in total 61 patients received 709 medicines. The medicine load for 1 patient was 11.6 medicines; 77% of the patients received from 11 to 15 medicines, 23% of the patients received from 6 to 10 medicines. The research did not reveal any patients who received ≤5 medicines. The results testified to a high level of polypharmacy. The next stage is the study of combinations of W and medicines presenting significant risk in terms of clinical safety. W was given in combination with the following medicines: heparin – 16% of patients; acetylsalicylic acid (AS acid) – 28% of patients; omeprazole – 21%; diclofenac – 13%; ciprofloxacin – 11%; metronidazole – 5%. It has been proved that the combinations of W and heparin, AS acid, and omeprazole are inadmissible, because they are life-threatening due to hemorrhage complications. Other unfavorable combinations of W have been revealed. They are: W + AS acid + omeprazole – 10% of patients; W + AS acid + ciprofloxacin – 4%; W + AS acid + diclofenac – 14%. These combinations significantly increase the risk of gastrointestinal bleeding.
Conclusion: The real clinical practice in hospitals revealed irrational prescription of medicines. The research has registered a high level of polypharmacy and dangerous combinations of W with other medicines. It has been proved that before prescribing treatment with W it is necessary to consider pharmacology genetics options, which are widely used worldwide. This kind of research has not been done in Kyrgyzstan. This determines the importance of personalized approach to pharmacologic therapy of W. This